AWARD NUMBER: W81XWH-15-1-0371

TITLE: “Elucidating the Role of Joint Disuse in the Development of Osteoarthritis following Return to High-Impact Loading

PRINCIPAL INVESTIGATOR: Douglas J. Adams, PhD

CONTRACTING ORGANIZATION: University of Connecticut
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REPORT DATE: October 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2016	Annual	30 Sep 2015 - 29 Sep 2016

4. TITLE AND SUBTITLE

Elucidating the Role of Joint Disuse in the Development of Osteoarthritis Following Return to High-Impact Loading

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-1-0371

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The joint disuse studies completed to date have reinforced and expanded upon important information regarding the influence of joint unloading on the articular cartilage tidemark. Joint unloading "activates" the otherwise quiescent tidemark within articular cartilage as well as ligament entheses. With this response evident in our joint disuse model within 2 weeks of joint unloading, it will be important to track this facet of the unloading-impact loading model through the proposed variations in recovery time versus return to vigorous activities imparting joint impact loads. The results of our remaining studies may provide clinically relevant information toward establishing reasonable bounds on time to return to activities following periods of joint disuse (such as required by sickness, injury, surgery, etc.). This may be particularly informative to individuals with occupations that require higher mechanical demands on joints.

15. SUBJECT TERMS
Osteoarthritis, cartilage, knee, joint, tidemark

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	15	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. INTRODUCTION

Joint immobilization and disuse, whether associated with treatment of joint injury or associated with bed rest, is known to be detrimental to joint health. Experimental studies using animal models of joint immobilization or reduced weight-bearing have shown that joint unloading for two weeks leads to degradation of the cartilage tissue. These relatively short periods of joint unloading may predispose some patients to developing long term arthritic problems if they return too quickly to activities that impart high forces to the joint in association with occupational demands, participation in high intensity athletic activities, or in the case of military personnel, the return to intense joint use associated with active duty. In fact, over 100,000 incidences of osteoarthritis (OA) were described in the Defense Medical Surveillance System from 1999-2008, and OA remains a leading cause of disability and medical discharge among service personnel (Cameron et al., 2011). While there are multiple causes of OA, **the goal of this study is to assess the contribution of return to high intensity activity after a period of joint disuse on the development of joint degeneration**. This study follows the responses of cells residing within knee joint articular cartilage, neighboring bone, and ligament tissues after a period of joint unloading followed by either normal ambulation and recovery or impact forces applied through the joint. Although unloading alone, or the impact force regimen alone, are not expected to initiate degradative cellular responses that would definitively be associated with long-term joint deterioration, **we hypothesize that following a period of disuse which is associated with a degree of recoverable degeneration of joint tissue, a premature return to high impact joint loading will elicit chronic degeneration. This project** capitalizes on mouse models of joint disuse and loading. Aim 1 examines the response to impact loading after disuse, as applied either in compression (Part A) or via a combination of compressive and shearing loads (Part B). Aim 2 examines the response to abnormal joint loading after disuse, as occurs following a destabilizing injury such as anterior cruciate ligament rupture.

2. KEYWORDS

Osteoarthritis, post-traumatic osteoarthritis, PTOA, cartilage, knee, joint degeneration

3. ACCOMPLISHMENTS

►What were the major goals of the project?

The major goals stated in the approved SOW are listed below with initially proposed target dates for completion and updated estimates for completion.

Major Goal	Timeline Proposed	Status/Estimated Completion
Animal use approvals	Months 1-3	Completed
Trouble shooting of histological staining and imaging	Not stated	Completed
Breeding and Growing mice necessary for Aims 1 and 2	Not stated	Completed, sufficient number of mice at necessary age now available and will continue to be available as needed
Specific Aim 1: Loading in Compression, Loading in Shear – Experiments studying temporal response to disuse followed by period of recovery and/or joint loading	Months 4-13	Preliminary studies completed January-May, 2016, refinements in experimental procedures completed May-September, 2016, Aim 1 formal studies initiated September 2016
Specific Aim 2: “ACL Transection Loading” – Experiments studying the temporal response to disuse and joint instability loading	Months 10-16	Studies to begin December 2016, completion of animal work February-March, 2017
Publications & Project Wrap-Up	Months 12-18	March, 2018 onward

►What was accomplished under these goals?

Our primary achievements to date have included successful breeding and growing of the large numbers of dual fluorescent reporter mice required for this study (a combination of types II and X collagen, indicating type II articular chondrocytes versus type X hypertrophic chondrocytes. We ran a complete pilot study outside of the animal numbers approved for this project, without the dual reporters but including mineralization labels and stains (toluidine blue, alkaline phosphatase) to refine all of the cryohistological sectioning and handling steps specific to this joint tissue-specific project. Most importantly, we also used the pilot project to find novel solutions to long existing problems related to mice slipping out of their tethers or learning unique ways to climb into food hoppers or tangle tethers into water bottles, all of which eliminate an animal from study. These efforts were rewarded in that, to date, we now have a 100% success rate for mice submitted to joint disuse via hindlimb unloading (tail suspension). Further details are provided in section 5 Changes/Problems.

The joint disuse studies completed to date have reinforced and expanded upon important information regarding the influence of joint unloading on the articular cartilage tidemark. Joint unloading "activates" the otherwise quiescent tidemark within articular cartilage as well as ligament entheses. This potential for activation was a key preliminary observation associated with joint unloading that we presented in the proposed work. With this response evident in our joint disuse model within 2 weeks of joint unloading, it will be important to track this facet of the unloading-impact loading model through the proposed variations in recovery time versus return to vigorous activities imparting joint impact loads.

Figure 1 demonstrates the utility of our cryohistological methods, whereby many signals, or channels, are obtained for single histological sections and can be viewed in various combinations to elucidate cellular activity and matrix changes. A complete description is provided in the figure caption below.

Description of Figure 1: Mouse Joint Unloading for 3 weeks

A: 6 µm thick sagittal cryohistological section through the medial condyles of a mouse knee joint. Three mineralization labels were delivered during hindlimb unloading on day 0 (Calcein, green), day 14 (Alizarin Complexone, red), and day 20 (Demeclocyline Hydrochloride, yellow) before euthanization on day 21.

B1: Magnification of box in panel A, showing mineralized tissue (white) and toluidine blue (TB) stained articular and calcified cartilage. The presence of all three mineralization labels in newly forming trabecular primary spongiosa "below" the epiphyseal growth plates provides assurance that mineralization labels were administered and active.

B2: Panel B1 without presentation of mineral or TB stained tissue, demonstrating the distribution of active mineralization captured by temporal delivery of the three fluorescent mineralization labels at days 0 (green), 14 (red), and 20 (yellow) of joint disuse.

B3: Panel B1 with the addition of red staining for alkaline phosphatase (AP) activity, an indicator of active osteoblasts and, when present or "activated" in articular chondrocytes, an indicator correspondent to transition to a hypertrophic phenotype (also see panels C4, D4).

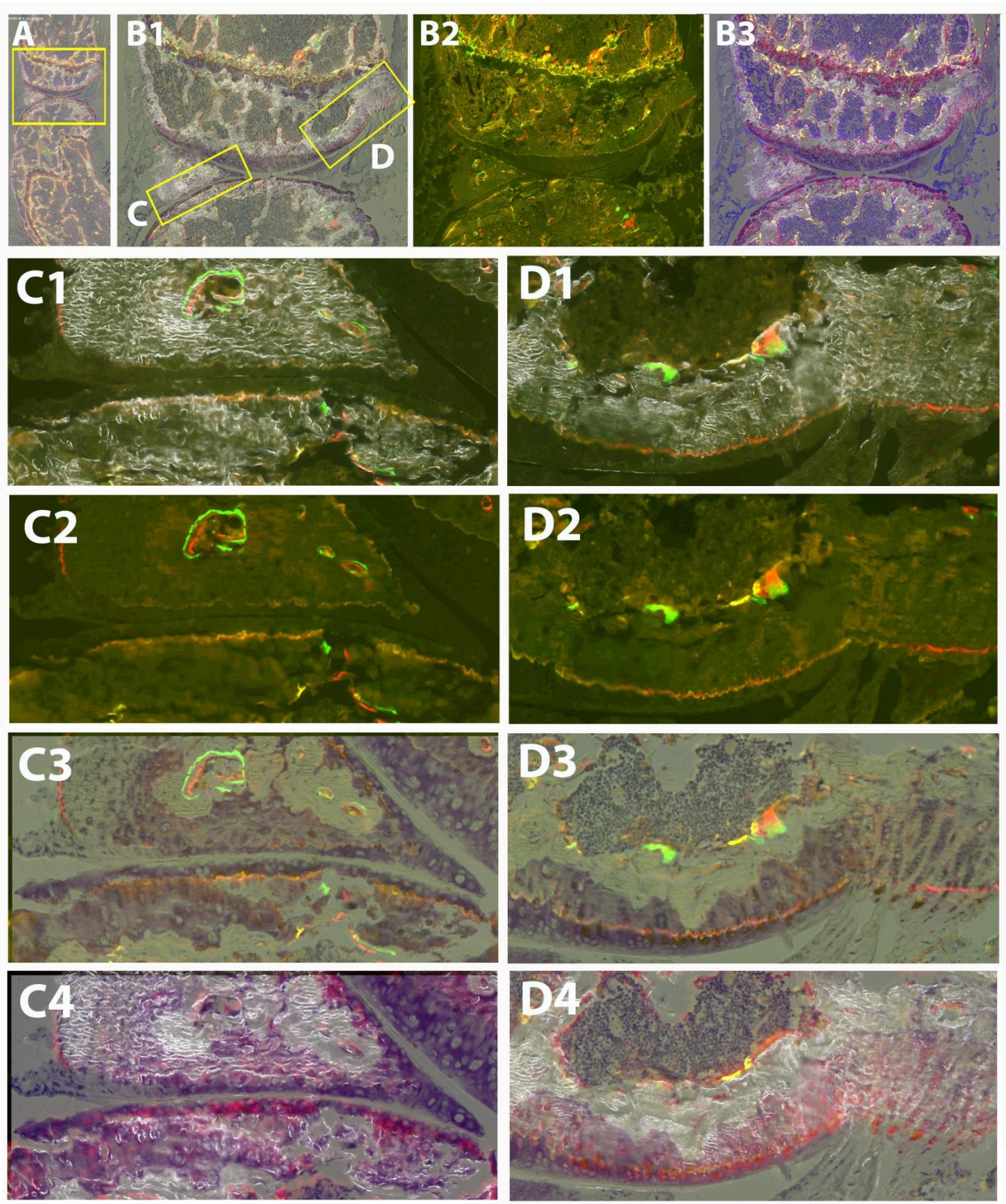
C1, D1: Abnormal active mineralization of articular cartilage tidemark (red & yellow labels) of the (C1) anterior tibial condyle and (D1) posterior femoral condyle and ligament enthesis, shown in relation to mineralized tissues (bone and calcified cartilage, white). Note the presence of calcein green label within bone, administered day 0, not present within the tidemark. Subsequent mineralization labels delivered on day 14 (red) and day 20 (yellow) after initiation of joint unloading are present within the tidemark, demonstrating an abnormal activation of that tissue "boundary."

C2, D2: Same panels as C1, D1 without mineralized tissue, clearly revealing active tidemark mineralization at days 14 (red) and day 20 (yellow) (yellow) of joint unloading, but not at day 0 (green, tidemark inactive).

C3, D3: Same panels as C2, D2 stained with toluidine blue to reveal calcified cartilage versus articular cartilage and bone, separated by the activated tidemark.

C4, D4: Alkaline phosphate (AP) expression (red) in chondrocytes indicating abnormal hypertrophic expansion beyond the tidemark into soft articular cartilage as well as into the unmineralized fibrocartilage zone of the enthesis. AP+ red chondrocytes are shown superimposed on image signal channels, or layers, for mineralized tissue and toluidine blue stain. In (D4) the mineralization label delivered one day prior to euthanization (day 20 of disuse, yellow) is shown in relation to the AP+ chondrocytes (indicating hypertrophic phenotype).

Figure 1: Mouse Joint Unloading for 3 weeks



►What opportunities for training and professional development has the project provided?

Dr. David Rowe has assisted Dr. Adams to become more proficient in processing and interpreting the digital multiple-signal fluorescence images produced by the cryohistological techniques. The next round of imaging will add the GFP reporters for articular chondrocytes and fibrochondrocytes of the enthesis that will be active and distinguish prehypertrophic and hypertrophic levels of chondrocyte differentiation.

Dr. Douglas Adams has trained Liping Wang in the special animal-related procedures required for hindlimb/joint unloading rodents via tail suspension.

►How were the results disseminated to communities of interest?

Nothing to report.

►What do you plan to do during the next reporting period to accomplish the goals?

A sufficient number of dual-GFP reporter mice (Col2A1 × ColX) now have been bred and grown to complete the goals of this project. All experiments of Aim 1 and Aim 2 will be completed during the next reporting period. We currently have a group of 14 mice that have completed the 2-week period of joint unloading and are distributed among the 7 experimental groups of Aim 1 (n=2/group), now undergoing joint loading regimens. We will continue to fill the 7 experimental groups of Aim 1 as well as the surgical instability model outlined in Aim 2 over the next several months to complete the project.

4. IMPACT

►What was the impact on the development of the principal discipline(s) of the project?

Our findings that a relatively short period (2-3 weeks) of joint unloading alone (without reloading) causes an activation of the mineralizing tidemark and hypertrophic properties of chondrocytes within articular cartilage and entheses of the murine knee joint is, by itself, indicative that joint disuse initiates/activates a change in joint physiology that warrants a temporal study of its resolution to homeostatic baseline. It will be important to answer this question regarding how long it takes to return to baseline, and what the effects of mild joint loading via ambulation versus more aggressive joint impact loading will be when imposed during the immediate post-disuse recovery period.

►What was the impact on other disciplines?

The cryohistological techniques which were improved and refined for this project, and the acute cellular response within articular cartilage and intra-articular ligament entheses, have provided a model system to our molecular biology colleagues for studying the role of individual molecules (genes) that are relevant to bone and joint tissue homeostasis. We are observing changes that are universally missed with traditional paraffin/decalcified histology. Methods for harvesting this tissue by laser capture microdissection (LDM) during the early stages of tidemark activation are being developed which will further expand the information provided by the joint unloading and loading models.

►What was the impact on technology transfer?

The combination of cryohistological methods, multiple-reporter mice, “all-in-one” histological slide examination, and joint unloading is an extension to joint tissues of the vast information and scientific rigor obtained using our cryohistology that we have demonstrated for bone histomorphometry. These methods are outlined in detail at our bone research website bonebase.org and within our recent video format publication (Dyment et al., J Vis Exp, (115), e54468, doi:10.3791/54468, 2016).

►What was the impact on society beyond science and technology?

As stated in our original grant application, we believe that the final scientific results of this study may provide translation information toward establishing reasonable clinical bounds on time to return to activities following periods of joint disuse (such as required by sickness, injury, surgery, etc.). This may be particularly informative to individuals with occupations that require higher mechanical demands on joints. A suggested recommendation for gradual return to activity might be suggested by the data, analogous to the current standard of care for traumatic brain injury (e.g., concussion), and toward a more cautious return to work, sport, and active military duty than is prescribed currently.

5. CHANGES/PROBLEMS

►Changes in approach and reasons for change

No significant changes in approach.

►Actual or anticipated problems or delays and actions or plans to resolve them

The extensive breeding scheme to produce dual-reporter mice has to be timed to availability of personnel. We initially started early and scaled back as the promise of filling the postdoctoral fellow position did not fit with annual clinical calendars due to the late award date. This possibility returned mid-year and was negotiated, but also could not materialize. Thus, we moved to our alternate approach of using trained staff rather themselves for this project, rather than the trainee whom they would have trained.

We ran a set of 10 mice through all aspects of joint unloading to reveal problems and refine methods associated with hindlimb unloading cages, tail traction, and histological methods. These mice were used outside of those approved for use in this study, allowing us to overcome several issues that would have thwarted our progress and scientific goals.

We observed that mice undergoing hindlimb/joint unloading were finding creative means to climb into food hoppers and water bottle fixturing, and thus loading their hindlimbs. We redesigned our custom roller-carriage cages to place the water bottles outside of the cage and replace food hoppers with new, purpose-built food hoppers that extend full height of cage and place food at the level of the mouse, preventing mice from climbing on the hopper.

We also experienced a loss of tail traction over time, such that some mice released from tail traction suspension and would thus be lost in the study. We consulted with Dr. Yasaman Shirazi at the Space Bioscience Division of NASA Ames Research Center in Moffett Field, CA, an experienced expert in prolonged tail suspension studies. Dr. Shirazi shared her protocols and, in particular, her key discovery to maintaining long-term tail traction by means of incorporating a specific additional adhesive (Amazing Goop®) within the tail traction harness. To date, we have categorically solved this problem for subsequent studies, without a single loss of tail traction.

The specimens generated from this “pilot” refinement work provided tissue for refining our histological cutting and staining methods specific to joint tissues.

►Changes that had a significant impact on expenditures

Due to the late grant award date and subsequent delay in funding (this proposal was in an “alternate” funding category for several months), we were not able to recruit our next postdoctoral surgical fellow from Dr. Shinro Takai’s institution due to the resulting mismatch in annual calendar availability. Although this resulted in lower expenditures to date for funding that postdoctoral salary, our solution toward completing the project is equivalent in both expertise and expenditures, employing the skills and experience of several

individuals within Dr. Rowe's "Service Core for Skeletal Research" core facility to work with Dr. Adams on the project. All funding awarded will be required to complete the remaining work.

►Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

There is no use of human subjects. All vertebrate animal procedures were approved 8/27/2015 under UConn Health IACUC #101102-0518. A subsequent annual review was approved on 7/28/2016 (attached in appendices).

►Significant changes in use or care of human subjects

Not applicable. No human subjects are used in this study.

►Significant changes in use or care of vertebrate animals

No significant changes in the use or care of vertebrate animals have been necessary or implemented.

►Significant changes in use or care of biohazards and/or select agents

No significant changes in the use or care of biohazards and/or select agents have been implemented.

6. PRODUCTS

►Publications, conference papers, and presentations

Although the following publication is not primarily a result of this study or its funding, the publication includes techniques that were developed for use in this study.

Dyment NA, Jiang X, Chen L, Hong SH, Adams DJ, Ackert-Bicknell C, Shin DG, Rowe DW: High-Throughput Multi-Image Cryohistology of Mineralized Tissues, J Vis Exp, (115), e54468, doi:10.3791/54468, 2016.

►Website(s) or other Internet site(s)

www.bonebase.org includes detailed methods of the cryohistological techniques used in this and related studies. These methods are reviewed in the JoVE publication video viewable at http://www.jove.com/video/54468/high-throughput-multi-image-cryohistology-of-mineralized-tissues.

►Technologies or techniques

The aforementioned refinements in experimental and cryohistological methods (Section 5. Changes/Problems) will be included in publication of the primary data at the completion of the study.

►Inventions, patent applications, and/or licenses

No inventions, patent applications, or licenses have resulted from this work.

►Other Products

Video tutorial - the aforementioned tutorial video which details the unique techniques of our cryohistological approach are viewable at http://www.jove.com/video/54468/high-throughput-multi-image-cryohistology-of-mineralized-tissues.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

►What individuals have worked on the project?

Name:	Douglas J. Adams
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	http://1.usa.gov/1JPqazR
Nearest person month worked:	3
Contribution to Project:	Dr. Adams refined experimental methods and performed studies toward completion of the project goals.
Funding Support:	This award

►Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Current active support for Dr. Adams and Dr. Rowe is included in the appendices.

Several changes in active support to Dr. Adams (PI) have occurred since the original submission of other support in May 2015. These changes in active support did not significantly impact the effort on the project that is the subject of this project report:

- Dr. Adams (PI, 25% effort) has been awarded R01 AR070879 from the NIH, award date 9/15/2016.
- Dr. Adams is no longer participating in NIH R01 AR064381 (Adams 5% effort).
- NIH R21 AR064941 funding (Adams 5% effort) has closed.
- Manufacturing Technical Assistance Program funding (Adams 5% effort) has closed.
- Connecticut Institute for Clinical & Translational Science (Adams 2% effort) has closed.
- Connecticut Space Grant Consortium (Adams 3% effort) has closed.

Several changes in active support to Dr. Rowe (co-I) have occurred since the original submission of other support in May 2015. These changes in active support did not significantly impact the effort on the project that is the subject of this project report:

- NIH R21 AR064941 funding (Rowe 5% effort) has closed.
- Dr. Rowe (PI) has reduced his effort on R01 AR063702 from 20% to 10%.
- NIH R01AR057076 funding (Rowe 5% effort) has closed.

►What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

►COLLABORATIVE AWARDS: Not applicable to this project.
►QUAD CHARTS: Not applicable to this project.

9. APPENDICES

i. Annual renewal of our animal protocol.
ii. Other support pages for Dr. Adams and Dr. Rowe.

Adams,Douglas

From: NoReplyUCSHC@topazti.net
Sent: Tuesday, August 02, 2016 9:30 AM
To: Rowe,David; Adams,Douglas; Fraize,Sara; Pohl,Alison; Wallace,Ronald; Chen,Li; Rydzik,Renata; Chuba,Lisa; Hoyt,Kelly; Wang,Liping; Chidambaram,Ramaswamy; Butler,Jessica; Dyment,Nathaniel; Cohn,Susan; Wu,Zhihua; Evans,Marisa
Subject: Annual Review for Animal Protocol 101102-0518 Approved on 7/28/2016

Hi, Dr. Adams ,

The annual review for your IACUC protocol 101102-0518, "Elucidating the Role of Joint Disuse in the Development of Osteoarthritis Following Return to High-Impact Loading", has been approved by the IACUC on 7/28/2016. This protocol will expire on 5/31/2018. The funding source(s) has/have been identified as Dept of Defense.

Species/amount approved for use include:

Mice #1

D- More than momentary pain or distress: 110

Potentially hazardous materials associated with this protocol include:
5-ethynyl-2'-deoxyuridine (edU) [C], Anesthetic Gas (Isoflurane, etc.) [Anesthetic gas], Demeclocycline (dcyc) [C], Transgenic animals [Tg/GT animals]

Please remember that any changes you may wish to make to your protocol, including the addition of qualified personnel, require that a modification be submitted to, and approved by, the IACUC prior to the implementation of those changes. It is the PI's responsibility to document all training given to each animal user on all procedures performed on animals. If you have animals with cage cards with an old protocol number, it is your responsibility to make sure those cage cards have been updated with the new protocol.

It is a condition of approval to use animals that the PI will report any adverse incidences (including unexpected morbidity and mortality) involving animals to the IACUC. This action is required by IACUC policy (http://acc.uchc.edu/policies/morbidity_mortality.html) in order to comply with federal regulations and laws.

Please review section 11 of your protocol to ensure that you are familiar with all the assurances you have agreed to. Please retain this email as it serves as your official approval letter.

The University of Connecticut Health Center has an Animal Welfare Assurance on file with the Office of Laboratory Animal Welfare (OLAW). The Assurance Number is A3471-01 and the effective dates are 4/1/14 - 4/30/18. It is your responsibility to notify the appropriate funding agency of this approval after review with the Office of Research and Sponsored Programs. Just-in-Time (JIT) notifications should be performed through the Office of Research and Sponsored Programs.

PLEASE NOTE: If your protocol involves the use of transgenic or gene targeted animals, an identification needs to be on the cage card. This must include at least one of the following: the full name of the line (e.g., such as the line name given by Jackson Labs), a "nickname" for the line (this must be identified in your protocol in the TgGT table), or the GMO number given to the animal.

ALSO NOTE: Please do not reply to this email, it will bounce back to you. Should you need help, please contact the

IACUC office at ooacc@uchc.edu.

If there is anything we can do for you in the future, please let us know. Thank you-

The IACUC Office

OTHER SUPPORT

ADAMS, Douglas J.
ACTIVE

DAMD W81XWH-15-1-0371 (Adams) 9/30/15 – 3/31/17 2.88 calendar
DOD/USAMRMC $140,756
Elucidating the Role of Joint Disuse in the Development of Osteoarthritis Following Return to High-Impact Loading

The goal of this project is to examine the temporal interaction of joint immobilization and return to activity on joint tissue degradation and recovery.

1 R01 AR 070879-01 (Adams) 9/1/16 – 8/31/21 3.0 calendar
NIH/NIAMS $420,422
Identification of Genes Regulating Bone Matrix Composition and Quality

The goal of this study is to identify genes that contribute to the regulation of bone matrix quality and to investigate how genetic background interacts with aging-related changes in bone quality.

4 R01 AR 063702-04 (Rowe, Ackert-Bicknell, Shin) 8/1/13 – 5/31/18 2.4 calendar
NIH/NIAMS $499,094
Skeletal Phenotyping of KOMP Mice

The goal of this collaboration with The Jackson Laboratory is to provide high-throughput skeletal phenotyping of gene knock-out mice generated within the Knock-Out Mouse Phenotyping Program.

5 R01 AR 064867-02 (Delany, Lee) 6/1/15 – 4/30/20 0.48 calendar
NIH/NIAMS $220,000
Role of MIR29 in Osteoclastogenesis

The goal of this project is to examine the role of microRNA29 in osteoclastogenesis utilizing sponge mice which inhibit miR29 expression in osteoclasts using a TRAP promoter.

5 R01 AR 055607-07 (Kalajzic) 7/1/15 – 5/31/20 1.08 calendar
NIH/NIAMS $220,000
Notch Signaling and Bone Fracture Healing

The goal of this project is to evaluate the effects of Notch signaling modulation *in vivo* using stage specific Notch gain- and loss-of-function models during fracture healing.

PENDING

1 R01 AR 070813-01 (Kalajzic) 12/1/16 – 11/30/21 1.2 calendar (yrs 2-5)
NIH/NIAMS $250,000
Growth Factor Based Enhancement of Bone Repair

The goal of this study is to provide better understanding on the interactions of PDGF and BMP2 during osteogenesis and bone healing.

1 R01 AR 070145-01 (Ackert-Bicknell, Adams) 4/1/17 – 3/31/22 3.0 calendar
NIH/NIAMS $118,115 (sub only)

Using Forward Genetics to Identify Genes Regulating Homeostatic versus PTH-Mediated Bone Architecture and Strength

The goal of this study is to identify genes that regulate bone form, function, and differential anabolic response to intermittent PTH.

OVERLAP

None

OTHER SUPPORT

ROWE, DAVID
ACTIVE

1R01AR064381-01 (Rowe, PI) 4/1/13 – 3/31/18 .48 calendar months
NIH/NIAMS $212,500
Targeted corrections of dominant mutations of type I collagen causing severe OI

A method for correcting the OI gene mutation in stem cells derived from affected adult individuals will be developed. It utilizes the latest techniques from stem cell biology and target gene correction, and it will evaluate a new approach to make the method more faithful and less expensive than the methods that are in current use. The other aspect of the grant is to demonstrate that the bone formed by these corrected stem cells in repairing bone defects in mice is equivalent to bone formed from normal stem cells and dramatically better that the bone formed from OI stem cells.

R01 AR063702 (MPI Rowe, Shin, Ackert-Bicknell) 9/1/13 – 5/31/18 1.2 calendar months
NIH/NIAMS $499,094
Skeletal Phenotyping of KOMP Mice

The goal of this collaboration with The Jackson Laboratory will be to provide high-throughput skeletal phenotyping of gene knock-out mice generated within the Knock-Out Mouse Phenotyping Program (Komp^2).

PR141985 (Adams) 9/30/15-3/29/17 .60 calendar months
USAMRAA $200,000
Elucidating the role of joint disuse in the development of osteoarthritis following return to high impact loading

R13 AR070574 (Rowe, PI) 9/1/16-8/31/17 .12 calendar months
NIH/NIAMS $15,000
Cryohistological assessment of the mineralized skeleton

This project will support a hands-on workshop to acquaint basic science research laboratories how to examine the activity of cells that participate in formation of the mineralized skeleton. Traditional methods are laborious and not amenable highly automated computer driven digital manipulation and image analysis. The new method enables multiple rounds of imaging from the same tissue section and computer processing of the entire workflow. It enables high throughput and consistent evaluation of experimental results across different laboratories and creation of image repositories accessible to the skeletal research community.

PENDING

1R21AR070991-01 (Rowe, PI) 12/1/2016-11/30/2018 .36 calendar months
NIH/NIAMS $158,100
Use of iPS-derived osteoblast and osteoclasts to discriminate between candidate genes obtained by WES as a contributor to human bone disease

A method for correcting the OI gene mutation in stem cells derived from affected adult individuals will be developed. It utilizes the latest techniques from stem cell biology and target gene correction, and it will evaluate a new approach to make the method more faithful and less expensive than the methods that are in current use. The other aspect of the grant is to demonstrate that the bone formed by these corrected stem cells in repairing bone defects in mice is equivalent to bone formed from normal stem cells and dramatically better that the bone formed from OI stem cells.

OVERLAP
None